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Information Processing in the Hippocampus and the Medial Prefrontal Cortex During Hippocampal Dependent and Independent Task: An LFP Analysis

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Information Processing in the Hippocampus and the Medial Prefrontal Cortex During Hippocampal Dependent and Independent Task: An LFP Analysis

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INTRODUCTION

It is well known that the hippocampus is important for the formation of memories, specifically episodic memories (Scoville and Milner, 2000). The discovery of "place cells" also drew attention to the role of the hippocampus in spatial navigation (O'Keefe and Dostrovsky, 1971; O'Keefe and Nadel, 1978). Place cells show selective firing for certain location and/or direction of a given environment, and have been found in different mammalian species (Rolls et al., 1989; Muller and Kubie, 1991; Nakazawa et al., 2002; Hough and Bingman, 2004; Yartsev and Ulanovsky, 2013). The human hippocampus shows activation as subjects solve virtual spatial navigation tasks (Maguire et al., 1998) and neurons show spatially organized representations (Burgess and O'Keefe, 2003; Etchamendy et al., 2012). Because of the spatial correlates of place cell activity, it has been suggested that the rat hippocampus may act as a cognitive map, providing the animal with a spatial representation of the environment (O'Keefe and Nadel, 1978).

Evidence for a hippocampal role in spatial navigation also comes from lesion studies (Morris et al., 1982, Cohen et al., 1971, Olton, 1977). Hippocampal damage impairs the effective use of spatial context information such as using landmarks to associate a location with either food reward, as in the plus-maze task, or safety, as in the Morris water maze (McDonald and White, 1993; Packard and McGaugh, 1996).

But not all navigation is spatial. Rats can use multiple strategies to navigate an environment (Tolman, 1946, 1947). Place strategies ("go there") rely on memory of the position of spatial landmarks to flexibly locate a goal, whereas response strategies ("turn right") rely on a series of fixed movements that compose an inflexible route. Findings of double dissociations of the effects of brain lesions in the hippocampus and the striatum indicates that place strategies are mediated by the hippocampal system and response strategies are mediated by caudate

nucleus, and they are not hippocampus dependent (Packard et al., 1989; Packard and McGaugh, 1992; McDonald and White, 1993; Kesner et al., 1993).

Based on this dissociation it is of interest to determine whether the hippocampus processes information differently when animal uses hippocampal dependent (spatial) and independent (response) strategies. Some studies reported that the hippocampus is acting differently when rats use these two strategies. For example, Maguire et al. 1998 showed difference in PET relative activity. However, this is a gross measure and does not provide information on physiology. Mizumori et al., 1996 showed that the hippocampal CA1 neurons of aged rats have more spatially selective place fields during spatial working memory task (hippocampal dependent) than during forced-choice task (hippocampal independent). This phenomenon was also observed in hippocampal hilar neurons of young animals.

However, it is difficult to draw definitive conclusions from this study. First, the different strategies and recording were conducted many weeks apart, allowing for changes in quality of recording. Second, the authors found that CA1 neurons of young animals didn't show any difference in spatial specificity between forced-choice task and spatial working memory task. There are other studies that demonstrated that the hippocampus processes information similarly regardless of whether the task is dependent upon the hippocampus. For example, Chang and Gold (2003) showed that the level of acetylcholine in the hippocampus remained the same even as the animal changed from a place strategy to a response strategy. Similarly, hippocampal CA1 neurons showed similar changes in firing patterns during both the delay (non-hippocampal) and trace (hippocampal) eye-blink conditioning task (Berger and Thompson 1978; McEchon and Disterhoft, 1997).

The goal of the current study was to see if the hippocampus shows similar LFP activity under hippocampal dependent and independent conditions. It is postulated that the oscillatory dynamics in the hippocampus support cognitive function in humans and rodents. Theta (4-12 Hz), the most prominent oscillation in the hippocampus, has been linked to both spatial navigation and mnemonic processes. Theta power has been shown to increase while an animal is learning a spatial task (Hasselmo, 2006). Theta power may increase during learning because it acts as a temporal organizer, synchronizing activity across multiple brain regions, allowing neurons to form assemblies. This would allow for chunking events and places together in time so that the participating neuronal assemblies can be tied together in a proper temporal and spatial context (Buzsaki, 2005). In addition to cognitive processes, volitional movement can modulate theta. Running speed has been shown to be positively correlated with theta (Vanderwolf, 1969; Hinman et al., 2011).

In addition to the hippocampus, the medial prefrontal cortex (mPFC) is essential for successful performance in learning and memory related tasks. Medial prefrontal cortex lesioned rats show impairment in goal and delay-based tasks (de Bruin et al., 1994, Kesner, 1989, Grannon et al., 1994) and also showed impairment in rule learning and decision making task (Miller et al., 2002). In fact the hippocampus and the medial prefrontal cortex may function as a unified network for certain cognitive processes (O'Reilly and Norman, 2002; Lee and Solivan, 2008; Benchenane et al., 2010). In imaging studies, both the hippocampus and prefrontal cortex are selectively activated during memory demanding tasks (Brewer et al., 1998; Stern et al., 2001; Schon et al., 2004;). Also, *in vivo* electrophysiology studies showed coordinated activities between the hippocampus and the medial prefrontal cortex (Hyman et al., 2005; Jones and Wilson, 2005; Siapas et al., 2005, Kim et al., 2011). For example, Hyman and colleagues (2005) showed mPFC cells fired with phase relationships to the hippocampal theta rhythm during spatial

navigation task. Kim and colleagues (2011) also showed spiking activities in both hippocampus and mPFC were phase-locked to theta rhythms during object –place paired association task and coherence in theta oscillation was maximal before entering a critical place for decision making.

In the current study we used plus maze in which a hippocampus dependent and independent navigating strategies can be contrasted. For the place task, rats were trained to go to the same "place" for a food reward regardless of the start arm (place strategy). For the response task, rats were trained to make either a right or left–hand turn for a food reward regardless of their start location (response strategy). While the rat was learning either a place or response task, theta (4-12Hz), low gamma (25-55Hz) and high gamma (65-90Hz) oscillations were monitored. Since activity levels and running speed are correlated with theta (Vanderwolf, 1969; Hinman et al., 2011) animals were also recorded during a well learned runway task which did not require learning or making a choice between arms. In addition to this, since the medial prefrontal cortex and the hippocampus is interacting and modulating each other during learning (Barker et al, 2007, Doeller et al, 2005, Jo et al, 2007, Lee and Kesner, 2003a), changes in theta power and coherence were measured both in medial prefrontal cortex and the hippocampus. The goal of this study was (1) to see if oscillations would be different under learning (maze) and non-learning (well-learned runway) conditions and (2) to see if they would be different when animal is learning a spatial or non-spatial task.

MATERIALS AND METHODS

Subjects

Twelve male Fisher 344 rats (Harlan) ~6 months old at the start of training were used. Rats were housed in a vivarium maintained at ~22°C and kept on a 12 h light/dark cycle (light on from 8 am to 8pm). Rats were housed individually in clear Plexiglas cages (46 x 20 x 23 cm) with pine bedding and ad libitum access to water. Rats were maintained at ~85% of their ad libitum weight during the experiment. All procedures were performed in accordance with the University of Connecticut's Institutional Animal Care and Use Committee.

Apparatus

A Plexiglas runway (120.7 x 10.2 cm) and modified version of the plus mazes were used for the study. The two plus mazes were constructed of black Plexiglas (112.4 cm long, 10.8 cm wide, 15.9 cm above a table surface). Four moveable black Plexiglas runways were constructed to form a perimeter around the plus maze. The plus maze for the place task was located in room C with white walls and posters, and the plus maze for the response task was located in room B with black walls. The runway was located in the room A which is in a third room outside of rooms B and C (Fig 1).

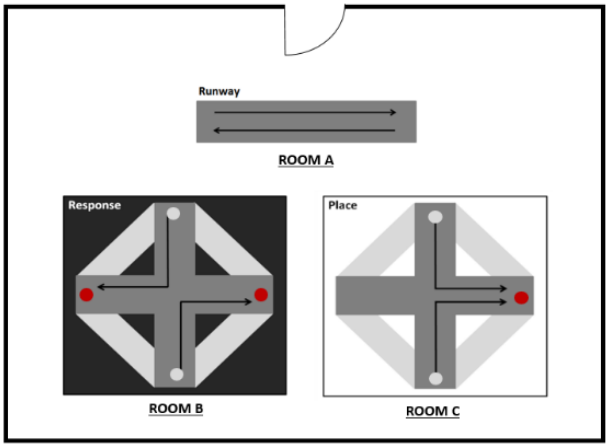

Figure 1. Schematic of behavioral testing room and place and response task. Plus maze for the response task and place task were located in room B and C respectively. Runway was located in the Room A which is located outside of the room B and C. Grey dots on the plus maze indicate potential start locations, red dots indicate goal locations. Arrows indicated the correct trajectory.

Pre-surgical Training.

Rats were trained to run back and forth on the runway for chocolate sprinkle rewards until they meet the criteria (50 runs within 10mins for two consecutive days).

Surgery

Each animal was deeply anesthetized with isoflurane (2.5~ 3.5%) in an induction chamber. The animal was then placed in a stereotaxic apparatus (ASI Instruments) and anesthesia was maintained by isoflurane (0.5~3%) afterward throughout surgery. The scalp was shaved and betadine was applied to the scalp and ophthalmic ointment to the eyes. The rat received the analgesic Metacam 1 mg/kg (s.c.) and penicillin (injectable, Durvet) 6600 units/kg (i.m.). An incision was made along the midline of the scalp and several small anchor screws were fastened to the skull. For ten animals, total five electrode arrays (each array contains 4 electrodes, tungsten wires; California Fine Wire) were implanted. One electrode array for the both hemisphere of prefrontal cortex (A/P – 3.2, L/M ± 0.75, D/V - 2.5 for prelimbic area, D/V – 4 for infralimbic area), two arrays for dorsal hippocampus (A/P + 4.0, L/M ± 2.5, D/V – 2.5) and other two arrays for ventral hippocampus (A/P + 5.3, L/M ± 5.3, D/V – 5.8). Two rats were implanted with electrodes only in dorsal and ventral hippocampus. Two ground screws were placed over the cerebellum to use as reference. After the surgery, the animals were placed in a clean cage with a heating pad until ambulatory, after which they were single housed in clean cages with bedding. The animals were allowed one week to recover before retraining and recording. The analgesic Metacam 1 mg/kg (oral) was given for the following 3 days of surgery.

Post-surgical Training.

After a week of recovery from surgery, the rats were retrained on the runway with head stage connected until they meet criteria (complete 50 runs within 15mins for two consecutive

days). The following day, the animals were recorded either on the place or the response maze task (counterbalanced across animals). On the first day of either task, the North and South arms were blocked, and rats were trained to run back and forth between East and West arms for chocolate sprinkle rewards. Once they were familiarized with running on the center track, actual plus maze training and the recording began. For the place task, rats were trained to go to a fixed "place" for a food reward (either east or west arm, counterbalanced) regardless of the start arm. For the response task, rats were trained to make either a right or left–hand turn for a food reward regardless of their start location. Each of the place and response tasks consisted of up to 50 trials per session. Each trial started when a blocker on the start arm was removed. Once rats made a choice, whether it was correct or not, perimeter runways connecting the arms were raised providing a path to the next start location. The rats were considered to have learned the plus maze task when they correctly completed nine trials in a row out of ten trials and showed 80% success rate (40/50 trials) for two consecutive sessions. The second day of two consecutive days was considered as a "post- criteria day" and the first day was considered as a "criteria day". And the day before criteria day was considered as "pre-criteria day". We included only the first 9 consecutive correct trials from each criteria days in the analysis. If animal learned the task so quickly and there was no pre-criteria day, we counted 9 trials backward from the criteria day trials. Once the rat reached criterion for the first plus maze task (either place or response task), the other place task was introduced in the second room. During the plus maze training, animals were given the runway task every other day (i.e. alternated daily between a training and familiar task day) (Fig 2). The rats were also recorded in the homecage for 5mins before and after the maze session.

Figure 2. Experimental paradigm. After a week of recovery from surgery, the rats were retrained on the runway with head stage connected until they meet criteria. The animals were then recorded while being trained either on the place or the response maze task (animals counterbalanced). Once the rat reached criterion for the first plus maze task (either place or response task), the other task was introduced in the second room. During the maze training, animals were given the runway task every other day. Runway data before post criteria day were used as control.

Recordings

Wide-band electrical activity was recorded (filters 1–2000 Hz, 3787 Hz) using Neuralynx Data Acquisition System. Light-emitting diodes attached to the headstage were tracked with an overhead camera (33 Hz) and monitored with the Neuralynx Video Tracker. Data were selected and analyzed off-line. All data were initially inspected visually (Neuraview, Neuralynx) to remove any segments of bad signal (e.g., due to a loose connection, bumping head). All signal analysis was conducted using Chronux toolbox and custom-written programs in MatLab (Mathworks). Data were then segmented using Neuralynx Video Tracker File Playback, Neuraview and Event Session Splitter to select specific behavioral epochs. The data was coded by maze segment and behavior, allowing for non-running segments like grooming, eating and waiting to be excluded from the analysis. Running speed for each trial was calculated as the positional difference between successive tracking samples and then low-pass filtered (cutoff = 0.25 Hz) to minimize the contribution of head movements and movement artifacts to the overall speed. Power spectraldensity estimates were obtained in MatLab using Chronux toolbox (mtspectrumc function, pad =1, taper = [2, 3]) (Mitra P, 2007, http://www.chronux.org). Each session was then blocked and power and frequency estimates were obtained for each segment of every trial.

Power estimates were obtained for the theta band (4–12 Hz) and represented as decibels (dB) relative to 1 uV. The corresponding frequency to maximum power was found for calculating peak frequency. Coherence values were taken from segments of each behavioral epoch concatenated into a single continuous string of data (Sabolek et al., 2009; Hinman et al., 2011, 2013; Penley et al., 2012, Schmidt et al., 2013, Jacobson et al., 2013, Jacobson et al., 2015). To accomplish this, a cross fading procedure was applied where both ends of each data segment (5% of averaged latency of each behavioral epoch over one session from each end) was ramped or faded respectively with a smooth B-spline window with continuous second-order derivates (Roark and Escabi, 1999). Adjacent start and end blocks from subsequent segments were then overlapped and morphed by adding the signals overlapping the ramp and fade regions. When the latency of a data segment exceeded 3secs, only the first and the last 1.5secs were analyzed. Coherence values (Bullock et al., 1990) for each channel pair were computed in Matlab using Chronux tool box (coherency function, pad =1, taper = [2, 3]) (Mitra P, 2007, http://www.chronux.org). To ensure that measured coherence values are not due to chance alone, a significance estimation procedure was devised by using custom written program in which the coherence estimate was compared with that of signals with identical magnitude spectrum but with zero phase coherence. For each channel pair, the cumulative distribution of the frequency-dependent coherence values is created by circularly phase shifting one signal in the pair by a random amount, calculating the coherence for the shifted signals, and bootstrapping the procedure 250 times (Efron and Tibshirani, 1994). This procedure guarantees that the signal spectrums are identical but have no linear association, because the phase or time information has been removed. The coherence distribution is used to determine a threshold for each frequency band, below which 95% of the shifted null hypothesis coherence values fell. Only regions of the non-shuffled signal coherences falling above the 95% threshold were considered significant (Sabolek et al., 2009; Hinman et al.,

2011, 2013; Penley et al., 2012). For each channel pair, the statistically significant area in the theta (4–12 Hz) band was calculated, and normalized by the frequency range (expressed as average coherence value per Hz). Average coherence values were normalized relative to the observed maximum for each frequency range, determined by calculating the significant areas in each frequency range for a channel pair where both elements of the pair are the same channel (C2 xx1.0 at all frequencies). The resulting normalized coherence value falls between 0 and 1.

Histology

Rats were sacrificed in a carbon dioxide chamber and transcardially perfused with 400 ml of saline followed by 400 ml of 4% fresh paraformaldehyde. The brains were extracted from the skull and stored in fixative before it was sliced. The brains were coronally sliced at 60 um on vibratome and stained with thionin.

The location of the electrode paths was examined and electrodes were categorized as

-Prefrontal : only the electrodes located in prelimbic area were included in analysis

-Dorsal Hippocampus: only the electrodes located in the dorsal SLM layer were included in analysis (before ML +/4, before DV-4.5).

-Ventral Hippocampus: only the electrodes located in area between CA1 pyramidal cell layer and the CA3 pyramidal cell layer (beyond ML +/4 , before DV-7).

RESULTS

Histological Verification of Electrode Positions

Total 5 arrays of electrodes were implanted in dorsal hippocampus, ventral hippocampus and mPFC in both hemispheres. (For 2 animals out of 12, only 4 arrays of electrodes were implanted in dorsal and ventral hippocampus in both hemispheres.) The location of electrode tips were verified histologically under the microscope (See Fig.3 and Table1) after all experiments were finished. For each animal, two electrodes with the best signal were selected per each brain area (dHipp, vHipp and mPFC) based on the location and electrophysiological quality.

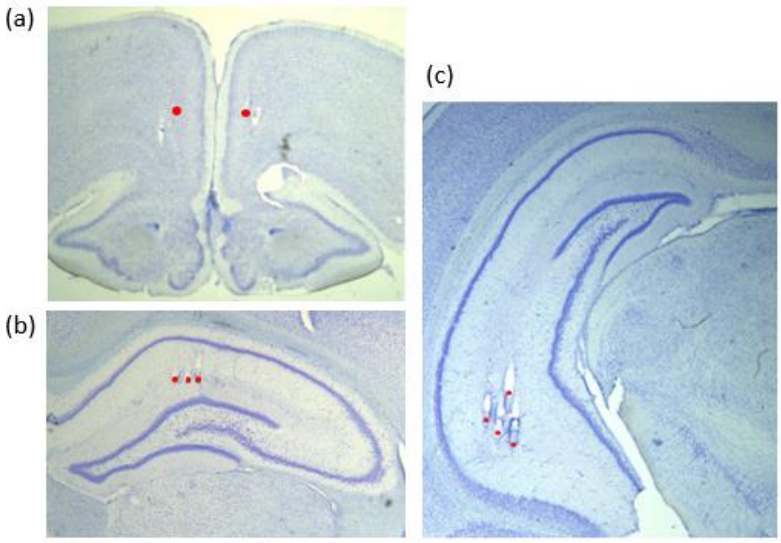

Figure 3. Example placements of mPFC (a), dHipp(b) and vHipp(c) electrodes.

Area	Specifics	Animals (n)	Electrodes (n)
Dorsal	CA1 SLM	7	13
Ventral	CA1 Apical Dedrite	5	4
mPFC	Prelimbic Area	10	20

Table 1. The location of electrode tips which are included for analysis. For dorsal hippocampus, only the electrodes located in CA1 SLM area were used. For ventral hippocampus, only the electrodes located in CA1 apical dendrite area were used. And for mPFC, only the electrodes located in prelimbic area were used. The number of animals and electrodes used for each area were counted.

Behavioral Results

Previous studies have shown that animals learn place task faster than response task (Korol and Pisani, 2015). We measured the number of trials required to reach the criteria when animals learned place and response task in different order. Animals learned place task significantly faster than the response task (t (10) = -2.488, p = 0.032*) when it was the first task learned. Once they learned the first task, there was no difference in learning speed between place and response task when learning the second (t (10) = -0.441, p = 0.669) (Fig. 4).

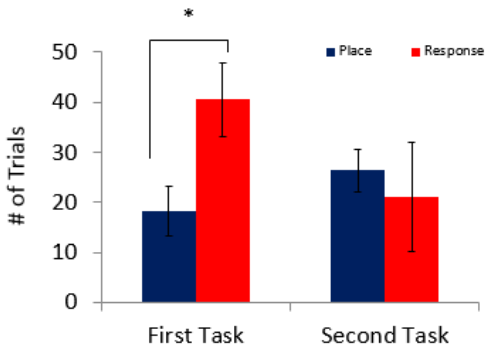

Figure 4. The number of trials to criteria was measured for place (blue) and response (red) task when animals learned those tasks in different order.

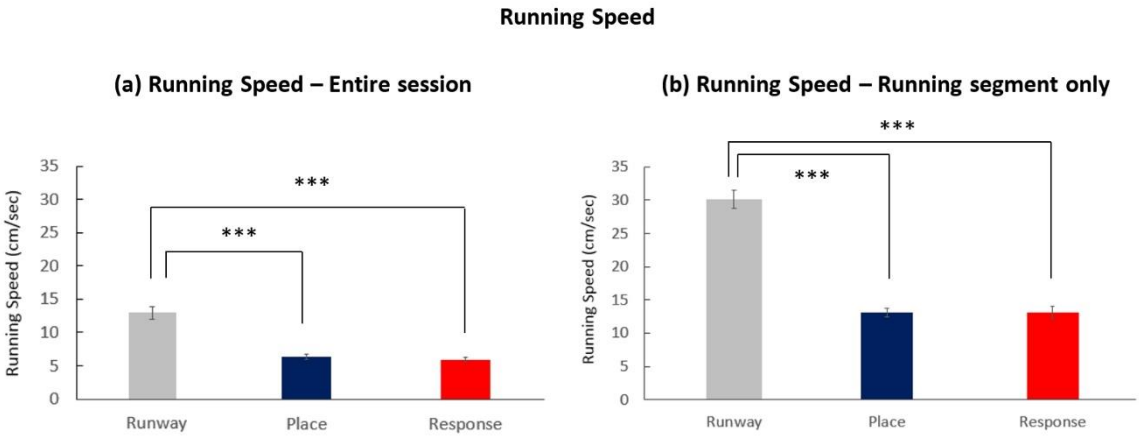

Figure 5. Running speed on familiar runway (gray), place task (blue) and response task (red). (a) Running speed for entire session. (b) Running speed only for running segment.

Theta power is modulated by running speed (Vanderwolf, 1969; Hinman et al., 2011). To dissociate the effects of running speed on theta power, running speed and its correlation with

theta power were measured. Running speed for entire session was measured for the runway, place and response task (Fig. 5a). Running speed on the runway was significantly higher than the place ($t(10)=-5.290$, $p=0.000$) and response maze ($t(11)=-5.978$, $p=0.000$). There was no difference in running speed between place and response task ($t(10)=0.677$, $p=0.514$).

To better compare the data on the plus maze to the runway, we only included the running segments on all three mazes for the analysis and excluded the grooming, eating and waiting behaviors. When examining only the running segments, running speed increased in all of three tasks as expected (Fig. 5b). Running speed on runway was higher than the place ($t(10)=10.645$, $p=0.000$) and response maze ($t(11)=14.156$, $p=0.000$). There was no difference in running speed between place and response task ($t(10)=-0.824$, $p=0.429$).

Theta Power

While the rat was learning either place or response task, the theta oscillation was monitored (Fig. 6 a&b). Since activity levels and running speed are correlated with theta (Vanderwolf, 1969; Hinman et al., 2011), animals were also recorded during a well learned runway task which did not require learning of making a choice between arms. To dissociate the effects of running speed on theta power, we used runway data as a within subject control and calculated relative power from it (Fig. 6 c). In both place and response task, there was no difference in hippocampal theta power between plus maze task and its runway control (dHipp on place task: $t(6)=-2.122$, $p=0.078$/ dHipp on response task: $t(6)=-0.503$, $p=0.633$/ vHipp on place task: $t(4)=-0.435$, $p=0.686$/ vHipp on response task: $t(4)=-0.566$, $p=0.601$). Only mPFC showed decreased theta power in the plus maze than the runway (Place maze vs Runway: $t(8)=5.030$, $p=0.001$, Response maze vs Runway:

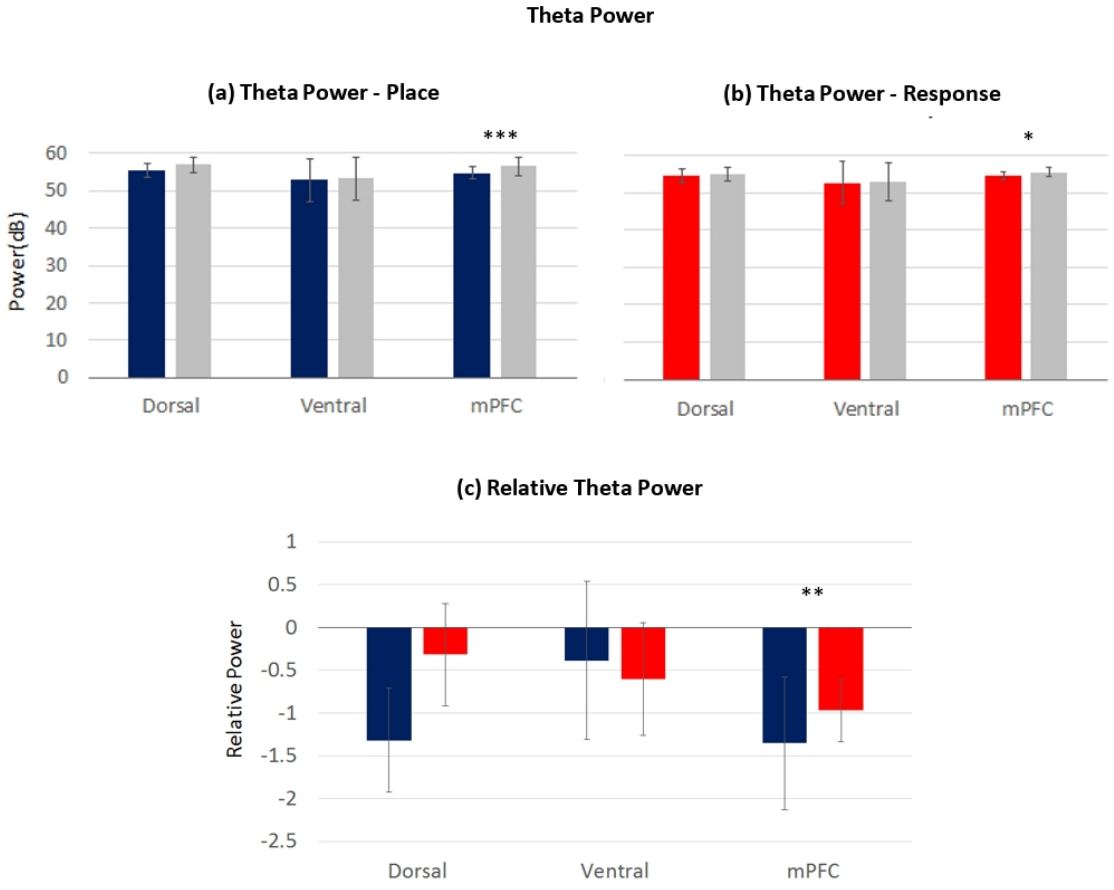

Figure 6. Theta (4-12Hz) power in three different brain areas (dHipp, vHipp and mPFC). (a) Absolute theta power during place task (blue) and its runway control (gray) (b) Absolute theta power during response task (red) and its runway control (gray). (c) Relative theta power ((a-b)/(|a|+|b|)x100, a = theta power on the plus maze , b = theta power on the runway) in place task (blue) and response task (red).

t(9)=-2.819, p=0.020). To contrast the effect of the place and response tasks and to control the effect of running speed, relative power to the runway control was calculated ((a-b)/(|a|+|b|) *100 , a = theta power on the plus maze, b = theta power on the runway) (Fig. 6 c). There was no difference in relative theta power between place and response task for both dorsal and ventral hippocampus (dHipp: t(6)=0.509, p=0.629 / vHipp: t(4)=0.189, p=0.859). However, theta in the mPFC decreased more during the place than in response task (t(8)=3.836, p=0.005).

Speed Modulation of Theta

To dissociate the effects of volitional movement and cognitive demands on theta power, the correlation values between running speed and theta envelope were examined during the plus maze task and its runway control. For dorsal hippocampus, running speed and theta envelope correlation significantly dropped during the place task compared to its runway control ($t(6)=-4.445$, $p=0.004$)(Fig. 7 a). However, there was no difference in correlation between the response task and its runway control ($t(6)=-1.154$, $p=0.292$). Considering that the theta power remained the same during the place task as compared with its runway control (Fig. 6 a), we can assume that theta power and running speed was decoupled in dorsal hippocampus during the place task

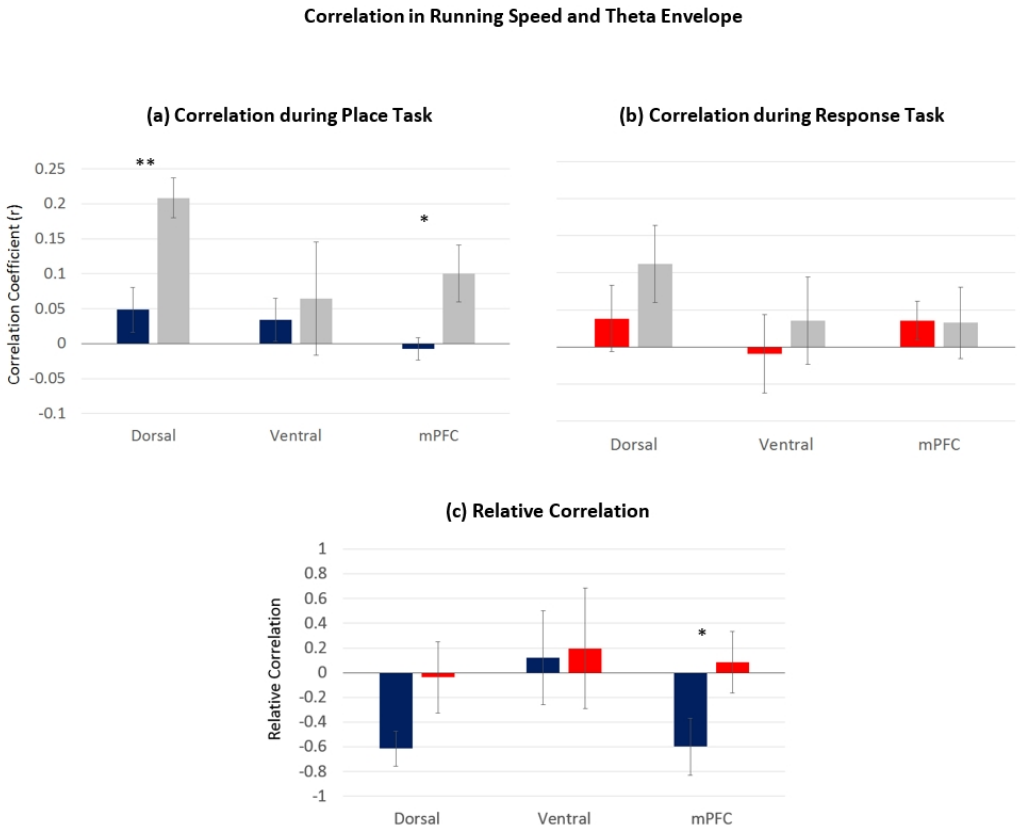

Figure 7. Correlation in running speed and theta envelope. (a) Correlation coefficient between running speed and theta envelope was calculated during place task (blue) and runway (gray). (b) Correlation in running speed and theta envelope during response task (red) and runway (gray). (c) Relative correlation score was calculated by (a-b) /(|a|+|b|)x100 (a = theta power on the plus maze , b = theta power on the runway). Blue and red represent place and response task respectively.

but not during the response task. The mPFC also showed decreased correlation during place task as compared to its runway control ($t(8)=-2.518$, $p=0.036$), however since the theta power also decreased during place task, (Fig. 6 a) decoupling didn't happened in the mPFC. The mPFC didn't show difference in correlation during response task ($t(9)=0.061$, $p=0.952$), and ventral hippocampus also didn't show difference between plus maze and runway control both during place and response task (during place task: $t(4)=-0.391$, $p=0.715$/ during response task: $t(4)=-0.421$, $p=0.696$). Relative correlation was calculated to make it easier to compare the effect on the place task and response task ($(a-b)/(|a|+|b|)$). There was no difference between place and response task in relative correlation for the dorsal and the ventral hippocampus (dHipp: $t(6)=-1.888$, $p=0.108$ / vHipp: $t(4)=-0.272$, $p=0.799$). However, there was a difference between place and response task found in the mPFC ($t(8)=-2.746$, $p=0.025$).

Theta Coherence

To examine how three different brain areas (dHipp, vHipp and mPFC) interact each other while they learn place and response task, normalized theta coherence was calculated as more than the 95% of shuffled signals within and in between the dorsal hippocampus, ventral hippocampus and the mPFC. Comparing the coherence on the plus maze with the one on the runway, overall there was no difference between plus maze and the runway both in the place and the response task (Fig. 8 a&b). However, there was a trend that the coherence within dorsal hippocampus increased during the place task ($t(5)=2.497$, $p=0.055$) and the coherence between the dorsal hippocampus and mPFC decreased during the response task($t(5)=-2.539$, $p=0.052$). To contrast the effect on two different plus maze tasks, relative theta coherence was calculated ($(a-b)/(|a|+|b|)$ x100)(Fig.8 c). Relative coherence within dorsal hippocampus was significantly higher during place task and the direction was opposite to the response task ($t(5)=3.007$, $p=0.030$). It means that the coherence within dorsal hippocampus increased while animals were

involved in spatial learning, but decreased when spatial learning was not required. Similar phenomenon was observed in dorsal-medial prefrontal coherence. Although difference between plus maze task and the runway was not significant, relative coherence was significantly different between place and response task ($t(5)=4.698$, $p=0.005$) since coherence changed in opposite direction during place task with response task (Fig. 8 a&b).

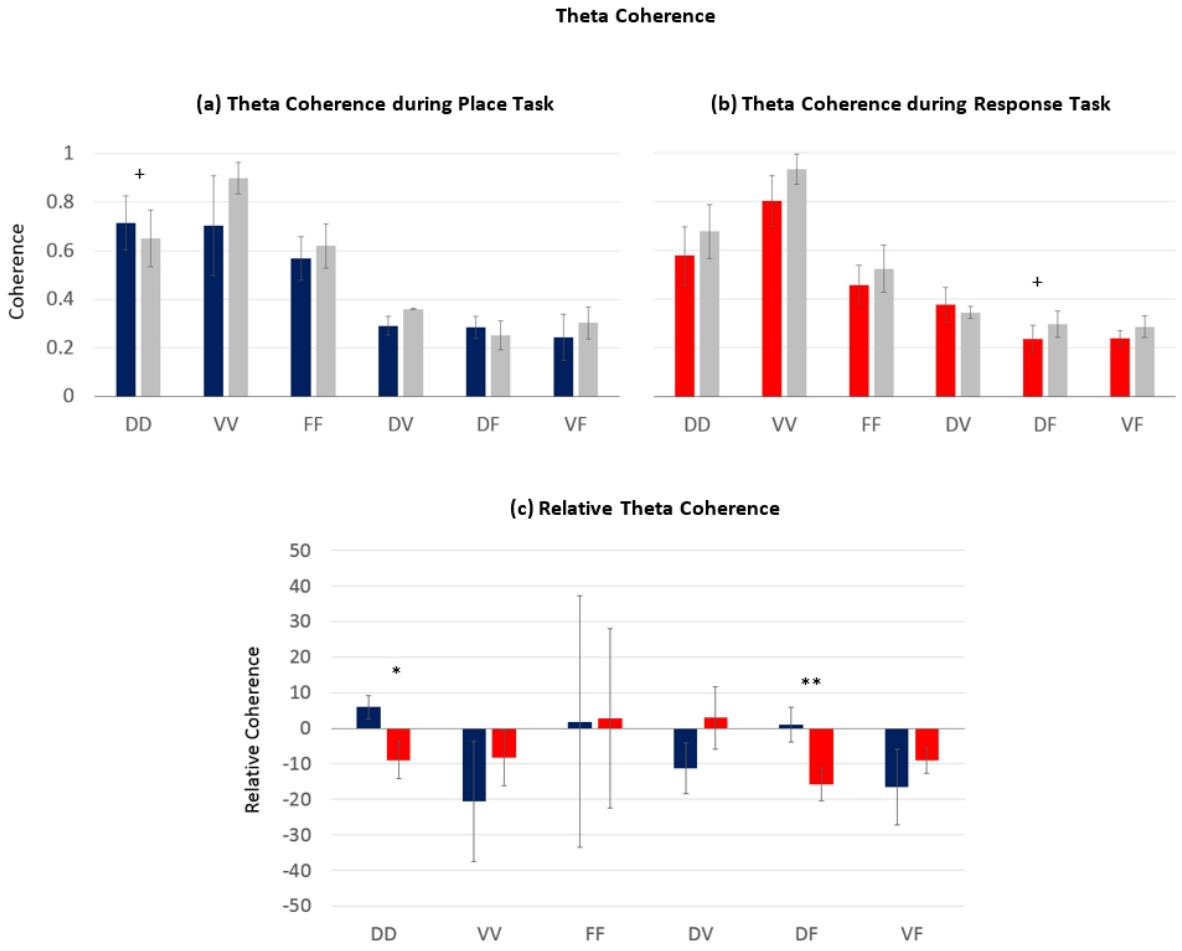

Figure 8. Theta coherence. (a) Normalized theta coherence was calculated within and in between the dHipp, vHipp and the mPFC during place task (blue) and its runway control (gray) (b) Normalized theta coherence was measure during response task (red) and its runway control (gray). (c) Relative theta coherence was calculated both in place task (blue) and response task (red) ((a-b)/(|a|+|b|)x100). DD: Coherence within dHipp. VV: Coherence within vHipp. FF: Coherence within mPFC. DV: Coherence between dHipp and vHipp. DF: Coherence between dHipp and mPFC. VF: Coherence between vHipp and mPFC.

Gamma Oscillations

While the rat was learning either a place or response task, low gamma (25-55Hz) and high gamma (65-90Hz) oscillations were monitored. Gamma oscillations in the hippocampus increase in amplitude during "theta behaviors" such as movement or sniffing (Bragin et al. 1995; Csicsvari et al. 2003) and correspond to memory and attention (Chrobak and Buzsaki, 1998a; Montgomery and Buzsaki, 2007; Colgin et al., 2009; Colgin and Moser, 2010;).

- Low Gamma Power and Coherence

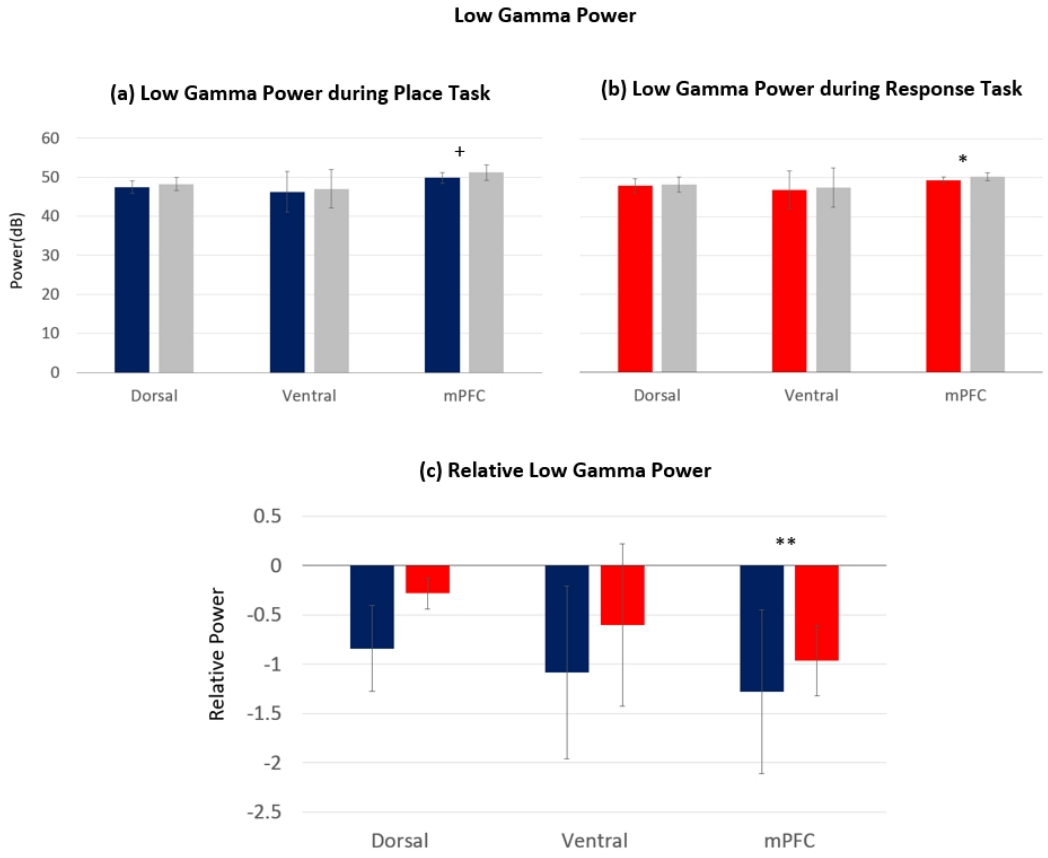

Figure 9. Low gamma (25-55Hz) power in three different brain areas (dHipp, vHipp and mPFC). (a) Absolute low gamma power during place task (blue) and its runway control (gray) (b) Absolute low gamma power during response task (red) and its runway control (gray). (c) Relative low gamma power ((a-b)/(|a|+|b|)x100, a = low gamma power on the plus maze , b = low gamma power on the runway) in place task (blue) and response task (red).

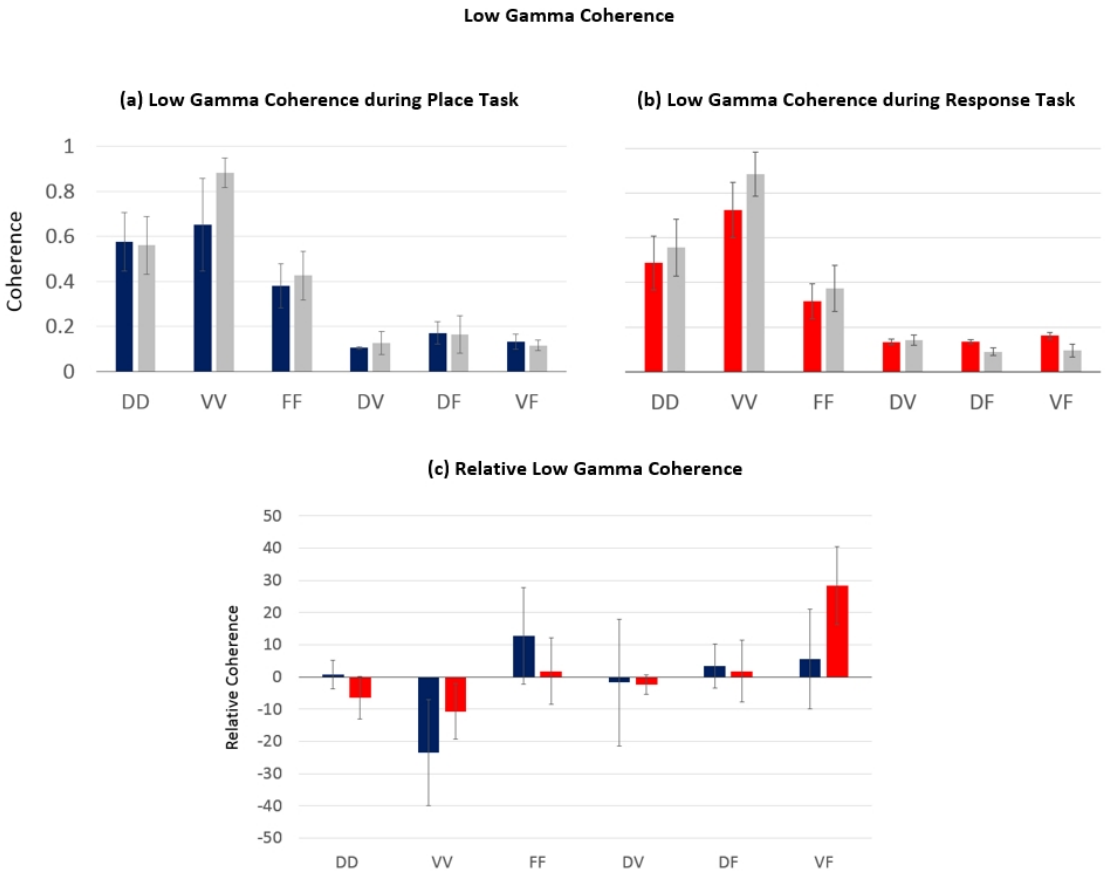

Figure 10. Low gamma coherence. (a) Normalized low gamma coherence was calculated within and in between the dHipp, vHipp and the mPFC during place task (blue) and its runway control (gray) (b) Normalized low gamma coherence was measure during response task (red) and its runway control (gray). (c) Relative low gamma coherence was calculated both in place task (blue) and response task (red) ((a-b)/(|a|+|b|)x100). DD: Coherence within dHipp. VV: Coherence within vHipp. FF: Coherence within mPFC. DV: Coherence between dHipp and vHipp. DF: Coherence between dHipp and mPFC. VF: Coherence between vHipp and mPFC

Results in low gamma power was very similar to the one in theta power. In both place and response task, there was no difference in hippocampal low gamma power between plus maze task and its runway control (dHipp on place task: t(6)=-1.880, p=1.109/ dHipp on response task: t(4)=-1.176, p=0.305/ vHipp on place task: t(4)=-0.435, p=0.686/ vHipp on response task: t(4)=-0.838, p=0.449). For mPFC, there was no difference in low gamma power between place task and runway (t(8)=-1.992, p=0.081) but power significantly decreased during response task

than during runway (t(9)=-2.819, p=0.025) (Fig. 9 a&b). For relative low gamma power, again only the mPFC showed the difference between place and response task (t(8)=4.160, p=0.003) (Fig. 9 c). We couldn't find any effects in both absolute low gamma coherence and the relative coherence (Fig. 10).

- High Gamma Power and Coherence

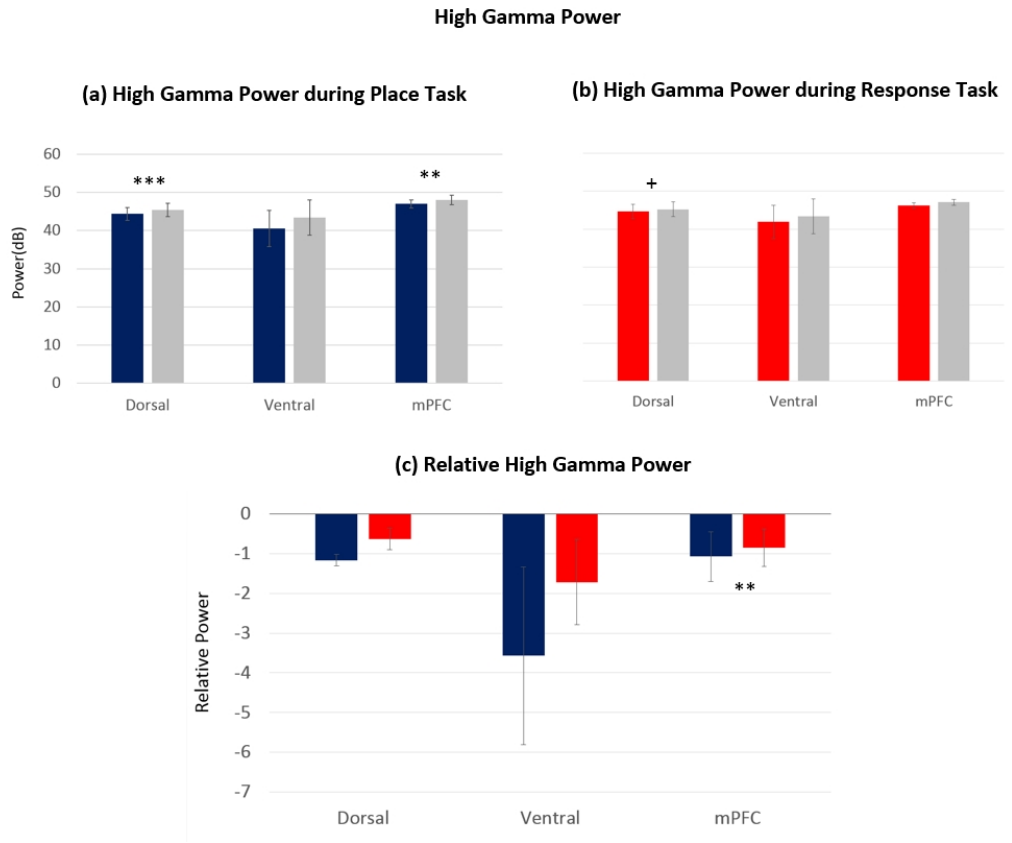

Figure 11. High gamma (65-90Hz) power in three different brain areas (dHipp, vHipp and mPFC). (a) Absolute high gamma power during place task (blue) and its runway control (gray) (b) Absolute high gamma power during response task (red) and its runway control (gray). (c) Relative high gamma power ((a-b)/(|a|+|b|)x100, a = high gamma power on the plus maze , b = high gamma power on the runway) in place task (blue) and response task (red).

Unlike theta and low gamma power, there was a significant difference in dorsal high gamma power between place task and its runway control (t(6)=-7.319, p=0.000) (Fig.11 a). Also, there was a similar trend is found during response task (t(6)=-2.338, p=0.058) (Fig. 11 b).

However, there was no difference in relative power between place and response task in dorsal hippocampus (t(6)=-1.872, p=0.110) (Fig.11 c). These results suggest that high gamma oscillation in dorsal hippocampus plays a role in learning in general, no matter it is spatial learning or not. mPFC also showed the difference in high gamma power on the place task as compared to the runway (t(8)=4.166, p=0.003), but not in the response task (t(9)=-1.847, p=0.098). These opposite directional changes were captured in relative power data and showed difference in place and response task (t(8)=3.884, p=0.005) (Fig.11 c). For ventral hippocampus, no significant differences were found both in absolute and relative data.

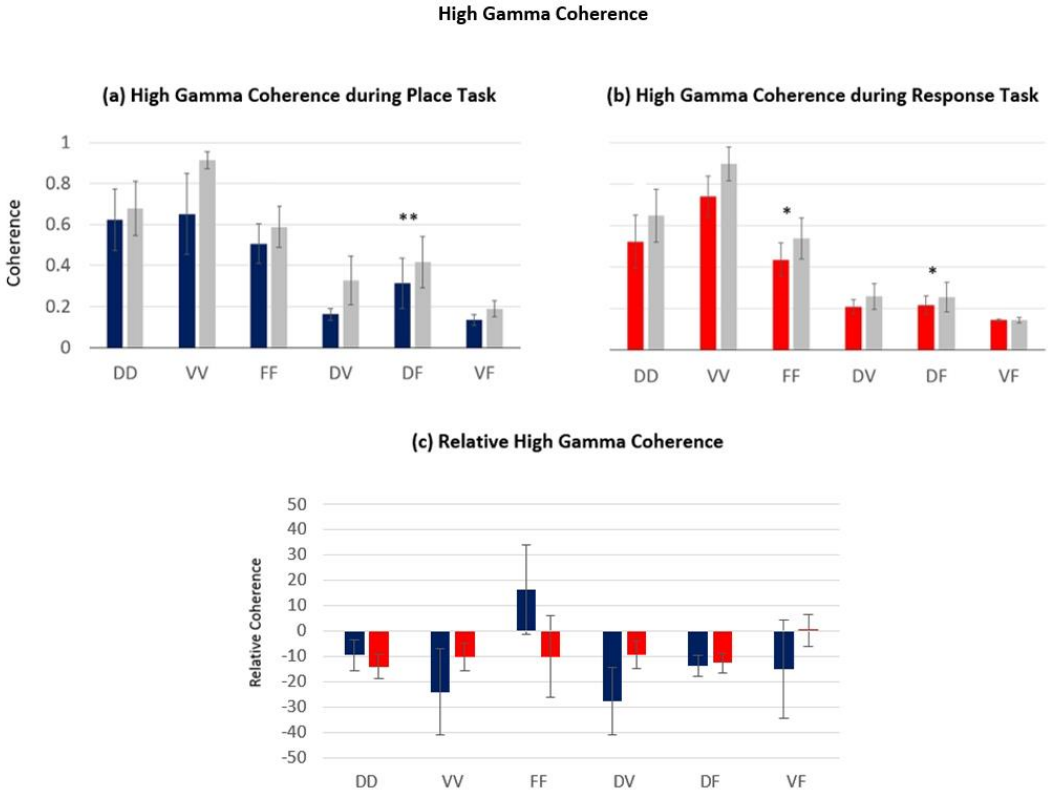

Fig 12. High gamma coherence. (a) Normalized high gamma coherence was calculated within and in between the dHipp, vHipp and the mPFC during place task (blue) and its runway control (gray) (b) Normalized high gamma coherence was measure during response task (red) and its runway control (gray). (c) Relative high gamma coherence was calculated both in place task (blue) and response task (red) ((a-b)/(|a|+|b|)x100). DD: Coherence within dHipp. VV: Coherence within vHipp. FF: Coherence within mPFC. DV: Coherence between dHipp and vHipp. DF: Coherence between dHipp and mPFC. VF: Coherence between vHipp and mPFC

It seems that the high gamma coherence show different activity when the dorsal hippocampus and the mPFC were involved. For example, coherence between dorsal hippocampus and the mPFC was significantly dropped on the plus maze as compared to the runway (place task: $t(5)=-4.757$, $p=0.005$/ response task: $t(5)=-2.894$, $p=0.034$). Also, coherence within the mPFC was significantly decreased or showed a trend of decreasing on the plus maze. (place task: $t(8)=-1.916$, $p=0.092$ / response task: $t(9)=-2.758$, $p=0.022$)(Fig.12 a&b). However, interestingly, those effects are gone and didn't show any difference between place and response task when we calculated relative high gamma coherence (Firg.12 c). These results suggest that the high gamma coherence plays a role in learning, either spatial or non-spatial learning, when the dorsal hippocampus and the mPFC were involved.

DISCUSSION

The goal of this study was to examine whether the hippocampus processes information differently, when animal learn a hippocampus dependent (spatial) and independent (response) task. In addition, given its importance in decision making, we also examined how the mPFC is interacting with the hippocampus. For this, rats' LFP activity in the hippocampus and the mPFC was monitored while animal performed place and response task on the plus maze.

The unique feature of our study was the use of two control situations. The familiar runway and learning a non-spatial task. Hippocampal theta power is positively correlated with running speed (Vanderwolf, 1969; Hinman et al., 2011), yet, it is also affected by cognitive/mnemonic demands (Klimesch, 1999; Düzel et al., 2010). Therefore, we used the closest runway data for each plus maze task as a within subject control. Since simply running back and forth on the familiar runway doesn't require cognitive load as compared to the plus maze

task, it could be a good control for effect of running speed on theta power. Also, we could control electrophysiological quality by using closest runway data for its paired plus maze data.

It should be noted that while animals learned the place task faster than response task when it was the first task, overall running speed was not different between place and response task. This was important because it confirmed that the difference found in running speed correlation, power and coherences between place and response task is derived from the difference in cognitive function, not from the difference in running speed.

Schmidt et al. (2013) reported that the correlation between theta power and running speed was uncoupled with increased cognitive demands in the dorsal hippocampus, but not in the ventral hippocampus. These results were replicated in our study. However, unlike Schmidt et al., uncoupling between dorsal theta power and running speed was only observed during place task, while they showed consistent results across tasks, regardless of hippocampal-dependent learning. This is probably because two studies used different way of control. Schmidt et al. broke down a trial into several segments and used "return" segment (running back to the start arm after animal made a decision and received food reward) as a control. Since return segments contains more cognitive loads than simple runway, such as feedback for rewards and more vigorous spatial navigation, it can diminish the difference in relative power between place and response task.

It has been controversial if the hippocampus processes information differently when animal uses hippocampal dependent (spatial) and independent (response) strategies. Many lesion studies have shown that the response task does not require the hippocampus (Jacobson et al., 2012; Packard and McGaugh, 1996). Also, hippocampal place cells differentiate between place and response strategies (Schmidt et al., 2012). However, other studies reported that the

hippocampus processes information similarly regardless of whether the task is dependent upon the hippocampus (Mizumori et al., 1996; Chang and Gold (2003); Berger and Thompson 1978; McEchon and Disterhoft, 1997; Guzowski et al., 2001; Schmidt et al., 2012; Schmidt et al.,2013). In our study, we could not find the difference in information processing between place task and response task only with the power of the hippocampal oscillations (theta, low gamma and high gamma). Also, coherence in low gamma and high gamma range could not differentiate the task effect. However, interestingly, theta coherence reflected the difference between place and response task, especially when the dorsal hippocampus and the mPFC were involved. It is possible that rather than local inputs or principal cell activity within the hippocampus, coactivity with mPFC has functional implications.

The medial prefrontal cortex (mPFC) is essential for successful performance in learning and decision making tasks (Miller et al., 2002). It has been suggested that the hippocampus and the prefrontal cortex (PFC) play key roles in utilizing contextual information for flexible strategy selection (Haddon and Killcorss, 2006; Horga et al., 2011). In our study, all three types of oscillations in mPFC showed difference in its power between place and response task. In addition, we also found that the high gamma oscillations in the dorsal hippocampus and its interaction with the mPFC play a role in general learning regardless of whether the task is dependent upon the hippocampus.

These findings suggest that overall the hippocampus itself process the information in the same way when animal learn a hippocampus dependent (spatial) and independent (response) task, while the mPFC process the information differently. However the hippocampus contrasts the difference between place and response task by interacting with mPFC within theta range.

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